REMARKS

STATUS OF THE CLAIMS

Claims 26, 28-31 and 33-44 are pending and were rejected under 35 U.S.C. § 103(a). In view of the following remarks and foregoing amendments, Applicants respectfully request reconsideration of the application.

DRAWINGS

Applicants note with appreciation that replacement Figure 6 is acceptable.

SEQUENCE LISTING

Applicants note with appreciation that the Sequence Listing is acceptable.

35 U.S.C. § 103

All of the pending claims remain rejected as allegedly obvious over U.S. Patent No. 6,015,686 (hereinafter "Dubensky"); Cella et al. (hereinafter "Cella") and U.S. Patent No. 5,736,388 (hereinafter "Chada") and WO 90/14090 (hereinafter "Gillespie"). Dubensky, Cella and Chada are applied as set forth in the previous Office Actions. Gillespie is cited for teaching dsRNA with complementing sequences from a vector construct to induce production of interferon. (Office Action, page 5).

Applicants traverse the rejection and supporting remarks.

The pending claims are directed to expression cassettes comprising a double stranded RNA formed by self-complementing sequences within the expressed RNA molecule.

As previously noted, there is no combination of Dubensky, Cella and Chada that render these claims obvious. Contrary to the Examiner's assertion that the references were argued "in isolation," Applicants again reiterate that the reference fail to teach all of the claimed elements individually and, accordingly, there can be no combination of these references that would result in the claimed invention. Applicants are well aware that if a single reference teaches all the elements of the claims, it will be applied in a rejection under 35 U.S.C. § 102. However, as previously set forth with regard to Dubensky, Cella and Chada, there is nothing in any of these references regarding double stranded RNA formed *in vivo* via self-complementation. Accordingly, even if there were some motivation to combine these references (which there clearly is not), there is no combination that establishes a *prima facie* case of obviousness because none teach the elements of the pending claims.

Gillespie, the newly cited reference, does not provide the motivation missing from Dubensky, Cella and Chada. In order to establish a *prima facie* showing of obviousness, the

onus remains on the Office to point to teachings or suggestions within the references themselves that would lead one of skill in the art to combine them as cited. *See, e.g., In re Rijckaert,* 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), emphasis added. The Federal Circuit has repeatedly held that there can be no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of filing. *See, e.g., Smiths Industries Medical Systems, Inc. v. Vital Signs, Inc.* 51 USPQ2d 1415, 1420-1421 (Fed. Cir. 1999). The relevant inquiry is whether there is motivation, reason or suggestion in the references that would lead one of ordinary skill in the art to combine the teachings of the references. *Id.*, emphasis added. Using an applicant's disclosure as a blueprint to reconstruct the claimed invention from isolated pieces of the references is impermissible. Not only must the suggestion be found in the references themselves, the burden remains on the Office to indicate, with particularity (*e.g.,* page, line or figure), where the motivation or suggestion to make the combination appears in the references. *See, e.g., In re Rijckaert,* 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), emphasis added. In the absence of the necessary motivation or suggestion in the references, the rejection is considered to be based on improper "hindsight reconstruction." (see, e.g., *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) and *In re Napier* 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) stating that "obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching, suggestion or incentive supporting the combination.").

Applying this law to the pending case, Applicants submit that a *prima facie* case of obviousness has not been, and indeed cannot be, established based on the cited references.

For the reasons of record and reiterated herein, Dubensky, Chada and Cella do not teach or suggest expression cassettes that form self-complementing dsRNA upon transcription *in vivo*, as claimed. Indeed, as acknowledged by the Office, Dubensky's double stranded RNAs are antisense RNAs. *See,* page 4, last paragraph of the Office Action. In addition, Applicants remind the Office that Dubensky clearly teaches that antisense RNA is the single "heterologous sequence" in the ELVIS vectors described. *See, e.g.,* col. 22, line 51-52. The Office has not pointed to anything in Dubensky that teaches an expression vector containing antisense RNA and another heterologous sequence encoding an antigen, as set forth in the claims. Despite this, the Office maintains that the motivation to combine Gillespie with the other references somehow derives from claims 9-16 of Gillespie, which relate to inducing interferon by administering a short dsRNA to a subject.

In fact, Gillespie contains no teaching or suggestion of expression vectors as claimed, namely vectors that express both dsRNAs formed *in vivo* by self-complementation and an additional nucleotide molecule that encodes an antigen. First and foremost, Gillespie fails to suggest production of dsRNAs *in vivo* via self-complementation. Rather, this reference teaches

that dsRNA should be formed *in vitro* under artificial conditions and, in addition, that this *in vitro*-formed dsRNA is preferably treated with RNase A prior to use (FIG. 3 and page 6, lines 5-10, emphasis added):

> Transcription of this plasmid as described in Figure 3 yields an RNA (structure [4] which **can be** self-annealed to produce the dsRNA shown as structure [5]. This hinged dsRNA can be used as it or can be trimmed with RNase to produce the dsRNA shown as structure ([6]), Figure 3.

Nor does Gillespie teach or suggest expression cassettes that include both self-forming dsRNA *in vivo* and sequences encoding an antigen. *See, e.g.,* Gillespie, page 6, line 26 to page 7, line 6, noting that expression vectors are unnecessary (emphasis added):

> It will also be obvious to those with ordinary skill in the art that oligonucleotides consisting of RNA polymerase promoters flanking inserts specifying the present invention can be synthesized, annealed and transcribed directly, **without cloning into a vector**. It will also be obvious to those with ordinary skill in the art that short dsRNAs can be chemically synthesized. **The essence of this invention lies in the structure and properties of the dsRNAs themselves**; this example is given to enable one with ordinary skill in the art to prepare short therapeutic dsRNAs of defined sequence.

Therefore, Gillespie does not provide any motivation to arrive at expression vectors as claimed. There is no teaching or suggestion of expression vectors as claimed, because Gillespie is directed entirely towards dsRNA formed *in vitro* and to methods of inducing interferon induction by administering only these already formed dsRNAs.

It is not enough to establish a *prima facie* case of obviousness that Gillespie teach dsRNAs formed by self-complementation *in vitro*. Gillespie must also provide the motivation to combine these teachings with those of Dubensky, Cella and Chada. *See,* cases cited above and *In re Gordon,* in which the Federal Circuit reversed the Board's finding of obviousness on the groups that the fact that the references were capable of modification to run the way the claimed device did, obviousness had not been established because there was no suggestion or motivation in the reference to make the modification. In the pending case, Gillespie not only fails to teach *in vivo* formation of dsRNA via self-complementation, this references also fails to provide the requisite motivation to combine its limited teachings regarding *in vitro* formation of dsRNA with Dubensky, Chada and/or Cella. Indeed, Gillespie is clear that expression vectors are not necessary and, when used to make dsRNA, it is only *in vitro*. There is no motivation in Gillespie

(or any of the other references) to modify Dubensky's expression cassettes as suggested by the Office.

Furthermore, in addition to the lack of motivation to combine the references as suggested, there is no combination of Dubensky, Chada, Cella and Gillespie that would lead the skilled artisan to expression cassettes as claimed, *i.e.,* cassettes that include an antigen-encoding sequence driven by an RNA polymerase II promoter and a sequence, which when transcribed *in vivo*, forms double stranded RNA via self-complementation, where the dsRNA induces the production of interferon. Indeed, substituting Gillespie's sequences into expression cassettes described in Dubensky, Chada and/or Cella would still not provide expression cassettes as claimed because none of these references teach expression cassettes including both dsRNA sequences and antigen-encoding sequences.

Moreover, and contrary to the Office's assertion, the induction of interferon by dsRNA as described in Dubensky and Gillespie does not provide a reasonable expectation that the claimed expression cassettes would function as claimed. *See, e.g.,* Office Action, page 5, citing claims 9-16 of Gillespie. As detailed above, the methods of claims 9-16, and indeed all the methods of Gillespie, involve administration of already formed dsRNAs. Dubensky's methods all involve antisense RNA. There is no teaching or suggestion in Gillespie that administering expression cassettes would result in formation of dsRNA via self-complementation *in vivo*; no teaching or suggestion that such expression cassettes would induce interferon production *in vivo*; and no teaching or suggestion that expression cassettes include additional coding sequences. Similarly, there is no teaching in Dubensky that dsRNA would form via self-complementation *in vivo* a and would induce interferon production. Accordingly, there is no reasonable expectation from the references that the claimed expression cassettes would function as claimed.

In sum, there is no motivation in the references to arrive at the claimed subject matter, no reasonable expectation of success, and no combination of these references that would render the pending claims obvious. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §1.16, §1.17, and §1.21, which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648, referencing Atty. Docket No. 2302-1631.

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